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Christian Gerges[1], Mario Gerges[1], Pierre Fesler[2], Anna Maria Pistritto[3], Nicholas P. Konowitz[1], Johannes Jakowitsch[1], David S. Celermajer[4] and Irene M. Lang[1]

Affiliations: [1]Dept of Internal Medicine II, Division of Cardiology, Vienna General Hospital, Medical University of Vienna, Vienna, Austria. [2]PhyMedExp, University of Montpellier, CNRS, INSERM and Dept of Internal Medicine Lapeyronie, CHU Montpellier, Montpellier, France. [3]Dept of Internal Medicine, Division of Cardiology, Ferrarotto Hospital, University of Catania, Catania, Italy. [4]Dept of Cardiology, Sydney Medical School, University of Sydney, Sydney, Australia.

Correspondence: Irene Lang, Dept of Internal Medicine II, Division of Cardiology, Medical University of Vienna, Währinger Gürtel 18–20, 1090 Vienna, Austria. E-mail: irene.lang@meduniwien.ac.at

ABSTRACT The commonest cause of pulmonary hypertension (PH) is left heart disease (LHD). The current classification system for definitions of PH-LHD is under review. We therefore performed prospective in-depth invasive haemodynamic phenotyping in order to assess the site of increased pulmonary vascular resistance (PVR) in PH-LHD subsets.

Based on pulmonary artery occlusion waveforms yielding an estimate of the effective capillary pressure, we partitioned PVR in larger arterial (R_{up}, upstream resistance) and small arterial plus venous components (R_{ds}, downstream resistance). In the case of small vessel disease, R_{up} decreases and R_{ds} increases. Inhaled nitric oxide (NO) testing was used to assess acute vasoreactivity.

Right ventricular afterload (PVR, pulmonary arterial compliance and effective arterial elastance) was significantly higher in combined post- and pre-capillary PH (Cpc-PH, n=35) than in isolated post-capillary PH (Ipc-PH, n=20). Right ventricular afterload decreased during inhalation of NO in Cpc-PH and idiopathic pulmonary arterial hypertension (n=31), but remained unchanged in Ipc-PH. R_{up} was similar in Cpc-PH (66.8±10.8%) and idiopathic pulmonary arterial hypertension (65.0±12.2%; p=0.530) suggesting small vessel disease, but significantly higher in Ipc-PH (96.5±4.5%; p<0.001) suggesting upstream transmission of elevated left atrial pressure.

Right ventricular afterload is driven by elevated left atrial pressure in Ipc-PH and is further increased by elevated small vessel resistance in Cpc-PH. Cpc-PH is responsive to inhaled NO. Our data support current definitions of PH-LHD subsets.

Introduction

The most common subset of pulmonary hypertension (PH) is PH due to left heart disease (LHD), resulting from left ventricular dysfunction (systolic and/or diastolic) and/or left-sided valvular heart disease [1]. PH-LHD is the consequence of an upstream transmission of elevated left atrial pressure (LAP). In 13% of cases with PH-LHD an increase in mean pulmonary arterial pressure (mPAP) occurs that is disproportionate to LAP due to an additional contribution of "pre-capillary" pulmonary vascular disease, which results in decreased right ventricular–pulmonary vascular coupling and has been associated with increased mortality [2–5]. Such patients can be identified by an elevated diastolic pulmonary vascular pressure gradient (DPG) ⩾7 mmHg. At present, the prognostic relevance of DPG has been both supported [5–11] and refuted [12–14]. Currently, PH-LHD is classified in the European Society of Cardiology/European Respiratory Society guidelines as either 1) "isolated post-capillary PH" (Ipc-PH; DPG <7 mmHg and/or pulmonary vascular resistance (PVR) ⩽3 Wood units (WU)) or 2) "combined post- and pre-capillary PH" (Cpc-PH; DPG ⩾7 mmHg and/or PVR >3 WU) [15].

The effective capillary pressure of the pulmonary circulation ($P_{c'}$) can be estimated based on the PAP decay curve after balloon occlusion (figure 1) [16]. Using $P_{c'}$, PVR can be partitioned into larger arterial (upstream, R_{up}) and small arterial plus venous (downstream, R_{ds}) components [16–19]. In healthy subjects PVR follows an almost equal distribution across the pulmonary circulation with ~60% R_{up} and ~40% R_{ds} [20]. In idiopathic pulmonary arterial hypertension (iPAH) there is a similar PVR partitioning pattern, yet a significant elevation in mPAP and $P_{c'}$ has been described. This has been explained by the fact that $P_{c'}$ is increased because small arterial remodelling extends to the capillary-venous compartment [16]. In chronic thromboembolic pulmonary hypertension (CTEPH) pulmonary artery occlusion waveform analysis has been employed to differentiate between central and peripheral pulmonary vascular obstruction [21, 22]. We sought to partition PVR at baseline and after inhalation of nitric oxide (NO) in patients with PH-LHD.

Methods

Study population

We prospectively enrolled 265 patients (figure 2). The ethics committee of the Medical University of Vienna approved the study and all patients signed informed consents (approval 1496/2012). Patients underwent a first diagnostic right heart catheterisation, vasoreactivity testing, pulmonary artery occlusion waveform analysis and left heart catheterisation, including coronary angiography and left ventricular end-diastolic pressure measurement, as previously described [4, 23]. Catheterisations were performed for various indications, mostly for the diagnosis of elevated systolic PAP (sPAP) on echocardiography, in patients with chronic heart failure and/or in patients with suspected PH, but also prior to valve replacements, percutaneous interventions and surgical procedures. A diagnosis of heart failure was

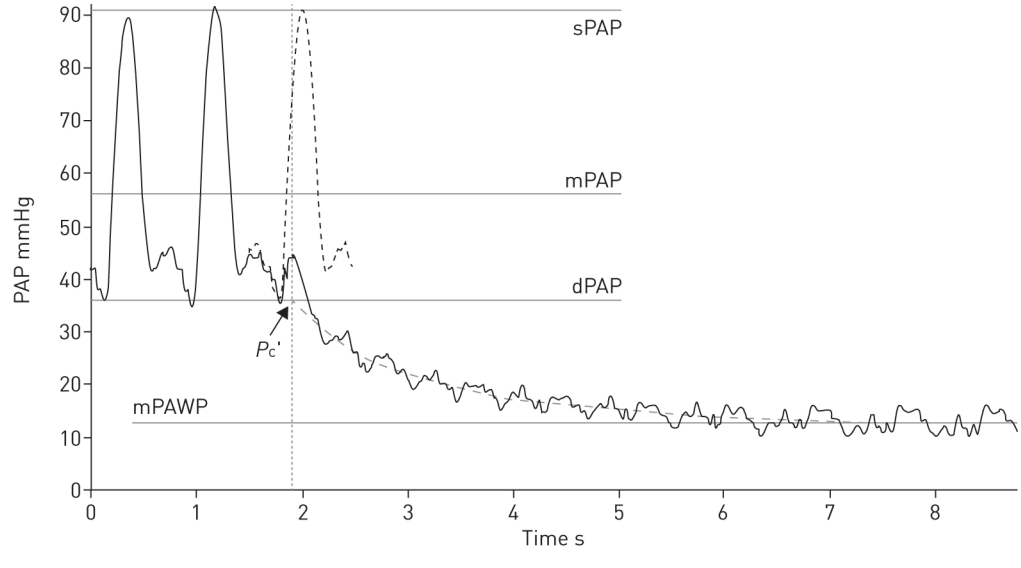

FIGURE 1 Pulmonary artery occlusion waveform. PAP: pulmonary arterial pressure; sPAP: systolic PAP; mPAP: mean PAP; dPAP: diastolic PAP. Pressure decay curve between the moment of occlusion (vertical dotted line) and the recording of mean pulmonary arterial wedge pressure (mPAWP) for the assessment of pressure in pre-capillary small pulmonary arteries and pulmonary capillaries ($P_{c'}$).

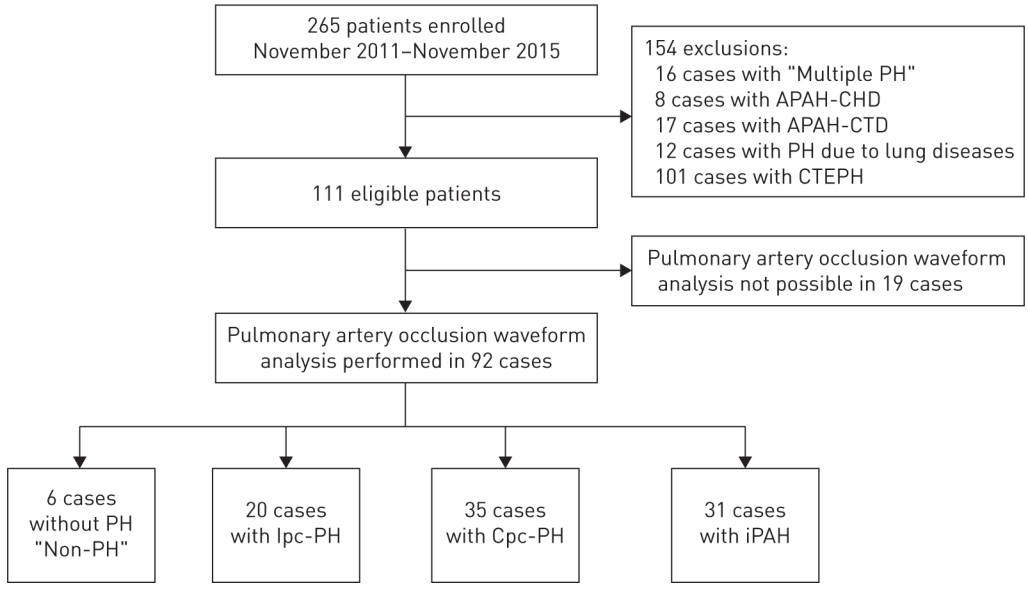

FIGURE 2 Patient disposition. PH: pulmonary hypertension; PAH: pulmonary arterial hypertension; APAH-CHD: PAH associated with congenital heart disease; APAH-CTD: PAH associated with connective tissue disease; CTEPH: chronic thromboembolic PH; Ipc-PH: isolated post-capillary PH; Cpc-PH: combined post- and pre-capillary PH; iPAH: idiopathic PAH. 265 patients were prospectively enrolled in our study. Pulmonary artery occlusion waveform analysis was not possible in 19 patients because of atrial fibrillation/arrhythmia. 92 patients were available for final analyses. Of those, six subjects had normal pulmonary haemodynamics ("Non-PH"), 20 patients had Ipc-PH, 35 patients had Cpc-PH and 31 patients had iPAH.

independently adjudicated according to the current heart failure guidelines of the European Society of Cardiology and the American College of Cardiology Foundation/American Heart Association [24, 25]. Patients with heart failure due to constrictive pericarditis and due to infiltrative, restrictive or hypertrophic cardiomyopathy were excluded. Patients were on specific and optimised heart failure treatments, at their physician's discretion, but none were taking PH-specific drugs.

Haemodynamic assessment and vasoreactivity testing

Haemodynamics were obtained at rest and during inhalation of 20 ppm NO (inhaled NO (iNO)). For haemodynamic assessment, a 7-French Swan-Ganz catheter (Edwards Lifesciences, Irvine, CA, USA) was inserted from a femoral or jugular venous approach. Mean right atrial pressure, right ventricular pressure, sPAP, diastolic PAP (dPAP) and mPAP, mean pulmonary arterial wedge pressure (mPAWP), and respective oxygen saturations, including inferior and superior vena cava saturations, were measured. Left ventricular end-diastolic pressure (LVEDP) was measured *via* femoral arterial access with a 7-French pigtail catheter (Cordis, Bridgewater, NY, USA). All pressures were recorded as averages of eight time–pressure integral derivations during several respiratory cycles using the Sensis system (Siemens, Berlin, Germany) [26]. Zero reference was at the mid-thoracic level [26]. Cardiac output (CO) was assessed in triplicate by thermodilution. With the catheter in the pulmonary artery, patients were given 20 ppm iNO *via* a continuous positive airway pressure mask under continuous flow oxygen at 2 $L \cdot min^{-1}$ (Pulmonox-Mini; Messer-Griesheim, Vienna, Austria) for 5 min before a complete haemodynamic assessment was repeated. iNO administration was continued during these measurements. A positive classic response to iNO was defined as a reduction of mPAP $\geqslant$10 mmHg to an absolute value of mPAP $\leqslant$40 mmHg with increased or unchanged CO [15]. A nonclassic response was defined as a reduction of mPAP $\geqslant$10 mmHg without a drop below an absolute mPAP value of 40 mmHg [27].

Haemodynamic definitions

The transpulmonary gradient (TPG) was calculated by subtracting mPAWP from mPAP. DPG was calculated as the difference between dPAP and mPAWP [2, 28, 29]. PVR was calculated by dividing TPG by CO and expressed in Wood units (WU; $mmHg \cdot min \cdot L^{-1}$). C_{PA} was defined as stroke volume divided by pulmonary pulse pressure (difference between sPAP and dPAP). The pulmonary vascular resistance–compliance time (RC-time; the product of PVR and C_{PA}, expressed in milliseconds) was estimated as previously described [30]. The effective arterial elastance (E_a) was calculated as the ratio of mPAP to stroke volume.

Partitioning of pulmonary vascular resistance

Pulmonary artery occlusion waveforms were recorded at 250 Hz during breath-hold at end-expiration over ~8 s. Pressure signals were filtered using a two-pole digital low-pass filter with a cut-off at 18 Hz. Measurements were performed in triplicate with an average difference in R_{up} of 4±2%. A biexponential fitting of the pressure decay curve between the moment of occlusion and mPAWP, with normalisation to mPAP, was performed in order to assess $P_{c'}$ (a surrogate of zero flow pressure (P_{zf})) (figure 1) [16, 31, 32]. Using $P_{c'}$, PVR was partitioned into larger arterial (upstream, R_{up}) and small arterial plus venous (downstream, R_{ds}) components. R_{up} was assessed as (mPAP–$P_{c'}$)/(mPAP–mPAWP)×100. Pulmonary artery occlusion waveforms from patients with atrial fibrillation and other forms of arrhythmia at the time of haemodynamic assessment were excluded (n=19) (figure 2).

PH definitions and subset classification

The PH guidelines distinguish the following haemodynamic definitions during measurements at rest, without iNO and oxygen: 1) "Non-PH" with mPAP <25 mmHg, 2) pre-capillary PH with mPAP ⩾25 mmHg and mPAWP ⩽15 mmHg, and 3) post-capillary PH with mPAP ⩾25 mmHg and mPAWP >15 mmHg [15].

Post-capillary PH was classified as either 1) Ipc-PH (mPAP ⩾25 mmHg, mPAWP >15 mmHg, DPG <7 mmHg and/or PVR ⩽3 WU) or 2) Cpc-PH (mPAP ⩾25 mmHg, mPAWP >15 mmHg, DPG ⩾7 mmHg and PVR >3 WU) [15, 33]. Moderate to severe and severe left-sided echocardiographic ventricular and valvular heart disease were assessed as probable causes of PH.

Ventilation–perfusion lung scintigraphy, multidetector computed tomography, lung function tests (including spirometry and diffusion capacity measurements) and pulmonary angiography were performed to exclude CTEPH, chronic obstructive pulmonary disease and interstitial lung disease. PAH associated with congenital heart disease, connective tissue disease or portal hypertension as well as CTEPH or PH due to interstitial lung disease (moderate to severe) and/or chronic obstructive pulmonary disease (Global Initiative for Obstructive Lung Disease stage 3 or 4) and/or obstructive sleep apnoea syndrome and simultaneous LHD were classified as "combinations of diagnoses" or "Multiple-PH". Patients with "Multiple-PH", PAH associated with congenital heart disease or connective tissue disease, PH due to lung diseases and/or hypoxia, and CTEPH were excluded from the study (n=154) (figure 2).

Statistical analysis

Adherence to a Gaussian distribution was determined using the Kolmogorov–Smirnov test. Normally distributed data were described as mean with standard deviation and the independent samples t-test was utilised to compare continuous variables between two groups, while the paired-sample t-test was used to compare differences within groups. In case of skewed distribution, data were described as median and interquartile range. One-way ANOVA with correction for multiple pairwise comparisons using the Bonferroni method was applied to assess differences across several groups. Qualitative variables were described as number and percentage. The strength of association between quantitative variables was measured with Spearman's rank correlation coefficient. Data were analysed with SPSS Statistics version 21 for Mac (IBM, Armonk, NY, USA). All p-values are results from two-sided tests, with significance inferred at $p<0.05$.

Results

Patients

92 patients fulfilled the pre-specified study criteria (figure 2). Six subjects had normal pulmonary haemodynamics ("Non-PH"), 31 patients were diagnosed with iPAH and 55 were classified as having PH-LHD: 20 with Ipc-PH and 35 with Cpc-PH (figure 2). Clinical characteristics are given in table 1. LVEDP was measured in all patients for validation of mPAWP. Bland–Altman analysis showed that LVEDP was on average 2.6 mmHg lower than mPAWP, with limits of agreement ranging from −7.6 to 2.4 mmHg in patients with PH-LHD. Larger differences between mPAWP and LVEDP were found in patients with mitral valve disease (one patient with severe mitral stenosis and four patients with mitral regurgitation).

Right ventricular afterload

Haemodynamics of the whole study population at rest and after iNO are given in table 2. Despite similar mPAWP (25.3±8.2 *versus* 21.1±3.4 mmHg; p=0.064), baseline right ventricular afterload was significantly higher in Cpc-PH (PVR 6.4±3.5 WU and E_a 0.8±0.4 mmHg·mL^{-1}) compared with Ipc-PH (PVR 3.1±1.3 WU; $p<0.001$ and E_a 0.6±0.2 mmHg·mL^{-1}; p=0.031). Right ventricular afterload was highest in iPAH (table 2, and figure 3a and b).

TABLE 1 Clinical characteristics

	"Non-PH"	Ipc-PH	Cpc-PH	iPAH
Subjects	6	20	35	31
Age years	67.9±16.9	65.3±12.8	66.3±11.2	46.9±17.9
Female	3 (50.0)	14 (70.0)	16 (45.7)	21 (67.7)
BMI kg·m^{-2}	26.3±6.1	29.4±6.4	27.3±5.4	25.3±5.0
NYHA functional class				
I	2 (33.3)	0 (0)	1 (2.9)	4 (12.9)
II	2 (33.3)	6 (30.0)	6 (17.1)	5 (16.1)
III	2 (33.3)	11 (55.0)	15 (42.9)	13 (41.9)
IV	0 (0)	3 (15.0)	13 (37.1)	9 (29.0)
Drug therapy				
Thiazide diuretics	1 (16.7)	3 (15.0)	7 (20.0)	0 (0)
Loop diuretics	0 (0)	11 (55.0)	27 (77.1)	10 (32.3)
Mineralocorticoid receptor antagonists	1 (16.7)	10 (50.0)	23 (65.7)	13 (41.9)
ACEI/ARB	3 (50.0)	13 (65.0)	23 (65.7)	3 (9.7)
Digoxin	0 (0)	0 (0)	6 (17.1)	0 (0)
β-Blockers	2 (33.3)	11 (55.0)	23 (65.7)	9 (29.0)
Ca^{2+} channel blockers	0 (0)	3 (15.0)	8 (22.9)	4 (12.9)
Heart failure				
Heart failure with preserved ejection fraction	0 (0)	14 (70.0)	26 (74.3)	0 (0)
Heart failure with reduced ejection fraction	0 (0)	3 (15.0)	6 (17.1)	0 (0)
Valvular heart disease[#]	0 (0)	3 (15.0)	3 (8.6)	0 (0)
Mitral regurgitation	0 (0)	3 (15.0)	1 (2.9)	0 (0)
Mitral stenosis	0 (0)	0 (0)	1 (2.9)	0 (0)
Aortic regurgitation	0 (0)	0 (0)	1 (2.9)	0 (0)
Tricuspid regurgitation				
Moderate to severe	0 (0)	1 (5.0)	4 (11.4)	5 (16.1)
Severe	0 (0)	4 (20.0)	13 (37.1)	4 (12.9)
Arterial hypertension	6 (100.0)	14 (70.0)	27 (77.1)	8 (25.8)
Stable ischaemic heart disease	1 (16.7)	4 (20.0)	11 (31.4)	0 (0)
Atrial fibrillation	1 (16.7)	9 (45.0)	19 (54.3)	1 (3.2)
COPD GOLD stage 1 or 2	2 (33.3)	4 (20.0)	8 (22.9)	0 (0)
Interstitial lung disease	0 (0)	0 (0)	0 (0)	0 (0)
Creatinine clearance <60 mL·min^{-1}	2 (33.3)	10 (50.0)	16 (45.7)	3 (9.7)
NT-proBNP pg·mL^{-1}	389.4 (38.7–538.1)	1757.0 (326.4–4167.5)	1272.0 (788.3–5298.8)	822.0 (234.1–2197.5)

Data are presented as n, mean±SD, n (%) or median (interquartile range). PH: pulmonary hypertension; Ipc-PH: isolated post-capillary PH; Cpc-PH: combined post- and pre-capillary PH; iPAH: idiopathic pulmonary arterial hypertension; BMI: body mass index; NYHA: New York Heart Association; ACEI: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; COPD: chronic obstructive pulmonary disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease; NT-proBNP: N-terminal pro-brain natriuretic peptide. [#]: moderate to severe or severe valvular heart disease.

Estimates of small pulmonary artery and capillary pressure

$P_{c'}$ was significantly different between groups (ANOVA; p<0.001) and significantly higher in Cpc-PH (31.3±8.2 mmHg) than in Ipc-PH (26.6±8.3 mmHg; p=0.026) and "Non-PH" (12.8±2.0 mmHg; p<0.001), but similar to values observed in iPAH (29.2±9.4 mmHg; p=0.365) (table 2). $P_{c'}$ was significantly higher than mPAWP in all groups. However, $P_{c'}$ to mPAWP gradients were larger in iPAH (mean 20.7 mmHg, 95% CI 17.2 to 24.3 mmHg; p<0.001) and Cpc-PH (10.2 mmHg, 95% CI 8.4 to 12.0 mmHg; p<0.001) than in "Non-PH" (3.2 mmHg, 95% CI 2.2 to 8.3 mmHg; p=0.009). In Ipc-PH, the difference between $P_{c'}$ and mPAWP was small (1.3 mmHg, 95% CI 0.7 to 1.9 mmHg; p<0.001). $P_{c'}$ correlated significantly with mPAWP in all groups. The strongest correlations were found in Ipc-PH (r=0.989; p<0.001) and "Non-PH" (r=0.900; p=0.037). Correlations were weaker in Cpc-PH (r=0.787; p<0.001) and iPAH (r=0.496; p=0.005).

During NO inhalation, a significant decrease in $P_{c'}$ was observed in Cpc-PH (−2.6 mmHg, 95% CI −5.0 to −0.2 mmHg; p=0.025) and iPAH (−4.4 mmHg, 95% CI −6.9 to −1.9 mmHg; p=0.007), while $P_{c'}$ increased significantly in Ipc-PH (3.4 mmHg, 95% CI 0.4 to 6.4 mmHg; p=0.014) and did not change in "Non-PH" (−1.4 mmHg, 95% CI −8.3 to 5.4 mmHg; p=0.458) (table 2).

Upstream resistance

R_{up} in Cpc-PH was similar (66.8±10.8%) to that seen in iPAH (65.0±12.2%; p=0.530) and "Non-PH" (62.4±4.6%; p=0.385). In contrast, R_{up} was significantly higher in Ipc-PH (96.5±4.5%; p<0.001) than in

TABLE 2 Haemodynamic characteristics at baseline and after inhaled nitric oxide (iNO)

	"Non-PH"		Ipc-PH		Cpc-PH		iPAH	
	Baseline	iNO	Baseline	iNO	Baseline	iNO	Baseline	iNO
Subjects	6		20		35		31	
Heart rate beats·min^{-1}	72.4±14.7	61.7±8.8	75.7±12.9	77.4±4.3	75.6±14.8	75.6±16.4	79.4±14.2	76.1±15.7[¶]
CO L·min^{-1}	5.9±1.0	6.0±1.0	5.6±2.2	5.4±1.4	5.0±1.3	5.5±1.4[¶]	4.6±1.1	4.9±1.2[¶]
SVR WU	14.2±0.6[#]	14.2±3.7[#]	16.0±5.3	16.6±7.2	18.3±6.9	17.0±5.9	19.0±5.8	19.6±5.0
mRAP mmHg	5.4±3.0[#]	7.2±1.9[#]	12.6±5.5[#]	12.9±7.8	15.8±4.9	15.9±7.6	9.5±4.7[#]	8.5±4.2[#]
mPAP mmHg	21.3±2.2[#]	20.4±2.1[#]	38.9±11.6[#]	40.8±13.9	48.1±12.6	42.2±11.6[¶]	54.9±13.6[#]	46.1±13.8[¶]
mPAWP mmHg	9.5±3.9[#]	11.0±2.9[#]	25.3±8.2	27.6±8.2[¶]	21.1±3.4	22.6±3.9[¶]	8.5±2.9[#]	9.5±4.0[#,¶]
LVEDP mmHg	11.0±4.1[#]	8.0±2.6[#]	23.0±7.3	24.8±8.5[¶]	19.1±5.5	20.2±3.9[¶]	9.6±3.3[#]	9.3±8.2[#]
$P_{c'}$ mmHg	12.8±2.0[#]	13.0±2.8[#]	26.6±8.3[#]	29.4±8.6[¶]	31.3±8.2	28.7±8.4[¶]	29.2±9.4	24.6±9.1[¶]
E_a mmHg·mL^{-1}	0.3±0.1[#]	0.2±0.0[#]	0.6±0.2[#]	0.6±0.3	0.8±0.4	0.6±0.3[¶]	1.0±0.4	0.8±0.4[#,¶]
PVR WU	2.1±0.4[#]	1.6±0.6[#]	3.1±1.3[#]	3.2±1.4	6.4±3.5	4.2±2.3[¶]	10.8±4.2[#]	7.9±4.2[#,¶]
C_{PA} mL·mmHg^{-1}	3.5±1.4[#]	5.4±1.8[#,¶]	2.4±0.9[#]	2.5±1.4	2.0±1.4	2.4±1.6[¶]	1.4±0.8[#]	1.8±1.0[¶]
RC-time ms	445±189[#]	493±204	405±152[#]	397±138	588±190	447±158[¶]	764±331[#]	693±200[#]
R_{up} %	62.4±4.6	62.8±7.6	96.5±4.5[#]	95.6±5.1[#]	66.8±10.8	74.8±13.6[¶]	64.5±12.3	71.3±10.7[¶]
TPG mmHg	12.5±3.5[#]	9.4±3.4[#]	18.0±7.5[#]	16.3±5.7[#,¶]	29.0±10.7	21.7±10.3[¶]	46.5±13.7[#]	36.3±14.9[#,¶]
DPG mmHg	3.5±3.9[#]	2.8±1.8[#]	3.9±2.2[#]	2.4±4.1[#]	14.2±4.9	7.4±8.0[¶]	28.0±11.6[#]	20.7±11.5[#,¶]

Data are presented as n or mean±SD. PH: pulmonary hypertension; Ipc-PH: isolated post-capillary PH; Cpc-PH: combined post- and pre-capillary PH; iPAH: idiopathic pulmonary arterial hypertension; CO: cardiac output; SVR: systemic vascular resistance; WU: Wood units; mRAP: mean right atrial pressure; mPAP: mean pulmonary arterial pressure; mPAWP: mean pulmonary arterial wedge pressure; LVEDP: left ventricular end-diastolic pressure; $P_{c'}$: effective capillary pressure; E_a: effective arterial elastance; PVR: pulmonary vascular resistance; C_{PA}: pulmonary arterial compliance; RC-time: PVR–compliance time (product of PVR and C_{PA}); R_{up}: upstream resistance; TPG: transpulmonary gradient; DPG: diastolic pulmonary vascular pressure gradient. [#]: p<0.05, compared with values in Cpc-PH using the independent samples *t*-test; [¶]: p<0.05, compared with baseline values within the same group using the paired samples t-test.

Cpc-PH (table 2 and figure 3c). R_{up} correlated strongly with DPG (r=−0.797; p<0.001) in PH-LHD (figure 4a). Correlations between R_{up} and TPG (r=−0.467; p<0.001), PVR (r=−0.495; p<0.001) and C_{PA} (r=0.279; p=0.039) were only weak (figure 4b–d).

During NO inhalation, R_{up} increased significantly in Cpc-PH (by 8.0%, 95% CI 2.2% to 13.8%; p=0.032) and in iPAH (by 6.4%, 95% CI 2.6% to 10.2%; p=0.005), indicating a decrease of distal vascular resistance (table 2 and figure 5c). In contrast, R_{up} did not change in Ipc-PH (−0.9%, 95% CI −4.0% to 2.3%; p=0.534) and "Non-PH" (0.4%, 95% CI −3.1% to 3.9%; p=0.974) (table 2 and figure 5c).

Response to iNO

Patients with Cpc-PH and iPAH showed significant improvements in CO, mPAP, PVR, C_{PA}, TPG and DPG during inhalation of NO (table 2, supplementary tables SA and SB, and figure 5a and b). In contrast, only an isolated increase of mPAWP occurred in Ipc-PH (table 2). In "Non-PH", C_{PA} increased significantly during NO inhalation (table 2). Three iPAH patients (9.7%) and three Cpc-PH patients (8.6%) fulfilled classic "haemodynamic responder" criteria. In nine patients with iPAH (29.0%), five patients with Cpc-PH (14.3%) and one patient with Ipc-PH (5.0%), mPAP dropped by ⩾10 mmHg but not ⩽40 mmHg (nonclassic response). None of the patients with Ipc-PH and "Non-PH" fulfilled classic responder criteria.

Supplementary tables SA and SB show relative changes from baseline under iNO in Ipc-PH, Cpc-PH and iPAH stratified by haemodynamic responder status. In classic responders with Cpc-PH (n=3), mPAP decreased by 33±17% (from 43.7±6.8 to 30.0±11.4 mmHg; p=0.036), CO increased by 33±18% (from 5.6±2.1 to 7.0±1.9 L·min^{-1}; p=0.018) and PVR decreased by 55±8% (from 5.1±2.4 to 2.1±0.6 WU; p=0.005). In iPAH (n=3), mPAP decreased by 42±5% (from 51.0±11.4 to 29.3±6.8 mmHg; p=0.021) and PVR decreased by 53±9% (from 11.2±5.1 to 5.6±3.6 WU; p=0.021), while CO remained unchanged (3±5%; from 5.6±2.1 to 7.0±1.9 L·min^{-1}; p=0.423).

In nonclassic responders with Cpc-PH (n=5), mPAP decreased by 4±13% (from 68.3±9.0 to 50.5±7.3 mmHg; p=0.002) and PVR decreased by 17±32% (from 11.9±4.8 to 5.7±3.2 WU; p=0.007), while CO remained unchanged (4±15%; from 4.2±1.2 to 4.4±1.4 L·min^{-1}; p=0.275). In iPAH (n=9), mPAP decreased by 7±9% (from 63.6±9.2 to 49.3±8.0 mmHg; p<0.001), CO increased by 9±13% (from 4.8±0.9 to 5.3±1.0 L·min^{-1}; p=0.016) and PVR decreased by 19±14% (from 11.4±2.0 to 7.5±2.1 WU; p<0.001).

In nonresponders with Cpc-PH (n=27), PVR decreased by 17±32% (from 5.3±2.3 to 4.3±2.1 WU; p=0.011), while CO remained unchanged (4±15%; from 5.3±1.1 to 5.5±1.2 L·min^{-1}; p=0.292). The

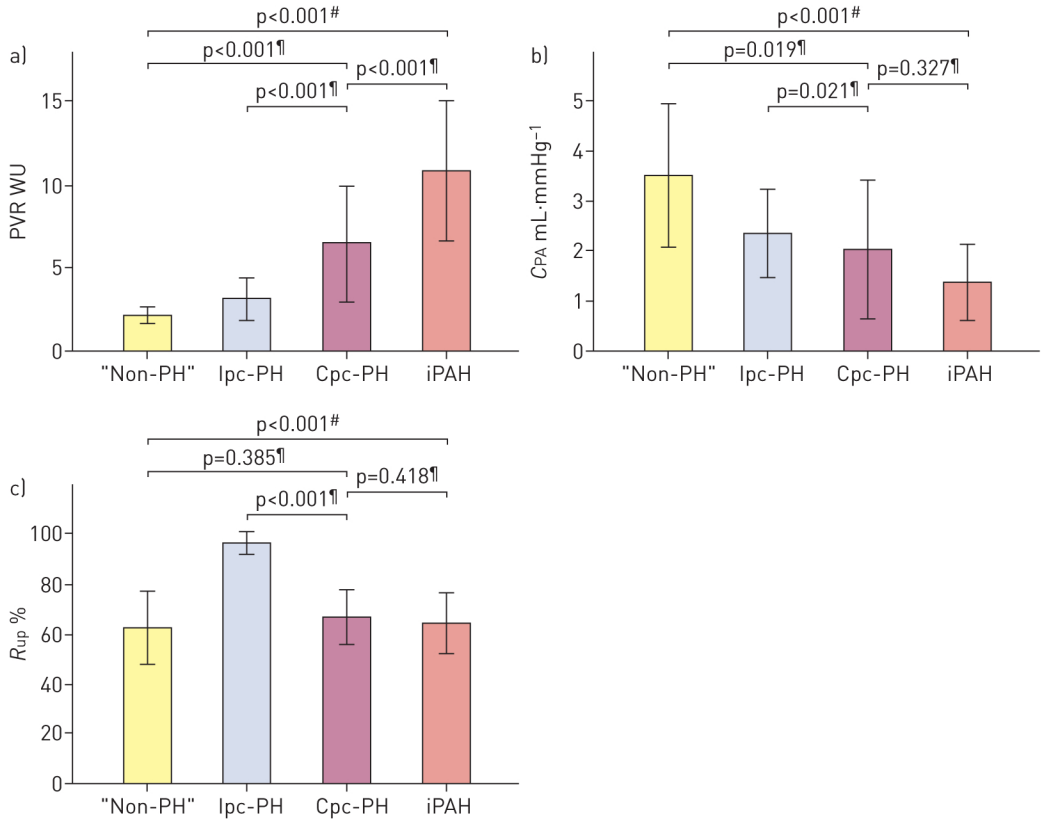

FIGURE 3 Right ventricular afterload and upstream resistance (R_{up}): a) pulmonary vascular resistance (PVR), b) pulmonary arterial compliance (C_{PA}) and c) R_{up} in patients with normal pulmonary haemodynamics (without pulmonary hypertension ("Non-PH")), isolated post-capillary PH (Ipc-PH), combined post- and pre-capillary PH (Cpc-PH), and idiopathic pulmonary arterial hypertension (iPAH). WU: Wood units. #: one-way ANOVA with correction for multiple pairwise comparisons using the Bonferroni method; ¶: independent samples t-tests.

decrease in mPAP (4±13%; from 44.3±11.0 to 42.3±11.2 mmHg; p=0.056) did not reach statistical significance. In iPAH (n=19), mPAP decreased by 6±9% (from 50.8±14.5 to 47.5±15.0 mmHg; p=0.004), CO increased by 9±12% (from 4.5±1.2 to 4.9±1.2 L·min^{-1}; p=0.007) and PVR decreased by 18±14% (from 10.3±5.3 to 8.5±4.9 WU; p=0.003).

Discussion

In this study, we examined detailed haemodynamics in PH-LHD patients and located the site of increased PVR by calculating R_{up} using the pulmonary artery occlusion technique. We also assessed changes in right ventricular afterload during inhalation of NO in PH-LHD. R_{up} is significantly lower in Cpc-PH than in Ipc-PH but resembles that in iPAH, consistent with the presence of pre-capillary pulmonary vascular disease in Cpc-PH. In contrast, the increase in PVR and PAP in Ipc-PH is driven by elevated LAP.

$P_{c'}$ is widely thought to reflect the pressure in small pulmonary arteries and capillaries [16–18], and should not exceed 16 mmHg in healthy subjects [20]. Values >20 mmHg have been associated with pulmonary oedema [20]. Concordant with previous studies using monoexponential [19] and biexponential fitting of the PAP decay curve after balloon occlusion [16], we found that $P_{c'}$ was markedly increased in iPAH compared with "Non-PH". $P_{c'}$ was significantly higher in Cpc-PH than in Ipc-PH (table 2). In Ipc-PH, the difference between $P_{c'}$ and mPAWP was negligible with a difference of 1.3±1.2 mmHg, and an almost perfect linear relationship between mPAWP and $P_{c'}$ (r=0.989; p<0.001), suggesting that $P_{c'}$ and mPAP elevation are determined by mPAWP. In contrast, the correlation between $P_{c'}$ and mPAWP was only moderate in Cpc-PH (r=0.787; p<0.001), similar to the findings in iPAH (r=0.496; p<0.001). $P_{c'}$ was significantly higher than mPAWP in Cpc-PH, suggesting an additional pre-capillary resistance component leading to an out-of-proportion increase in PAP (figure 6).

We located the site of increased PVR in Cpc-PH by partitioning PVR into R_{up} and R_{ds} using the pulmonary artery occlusion technique. Cpc-PH showed the same pattern of PVR partitioning as iPAH (figure 3c), with ~60% R_{up} and ~40% R_{ds}. The present findings are in agreement with histological

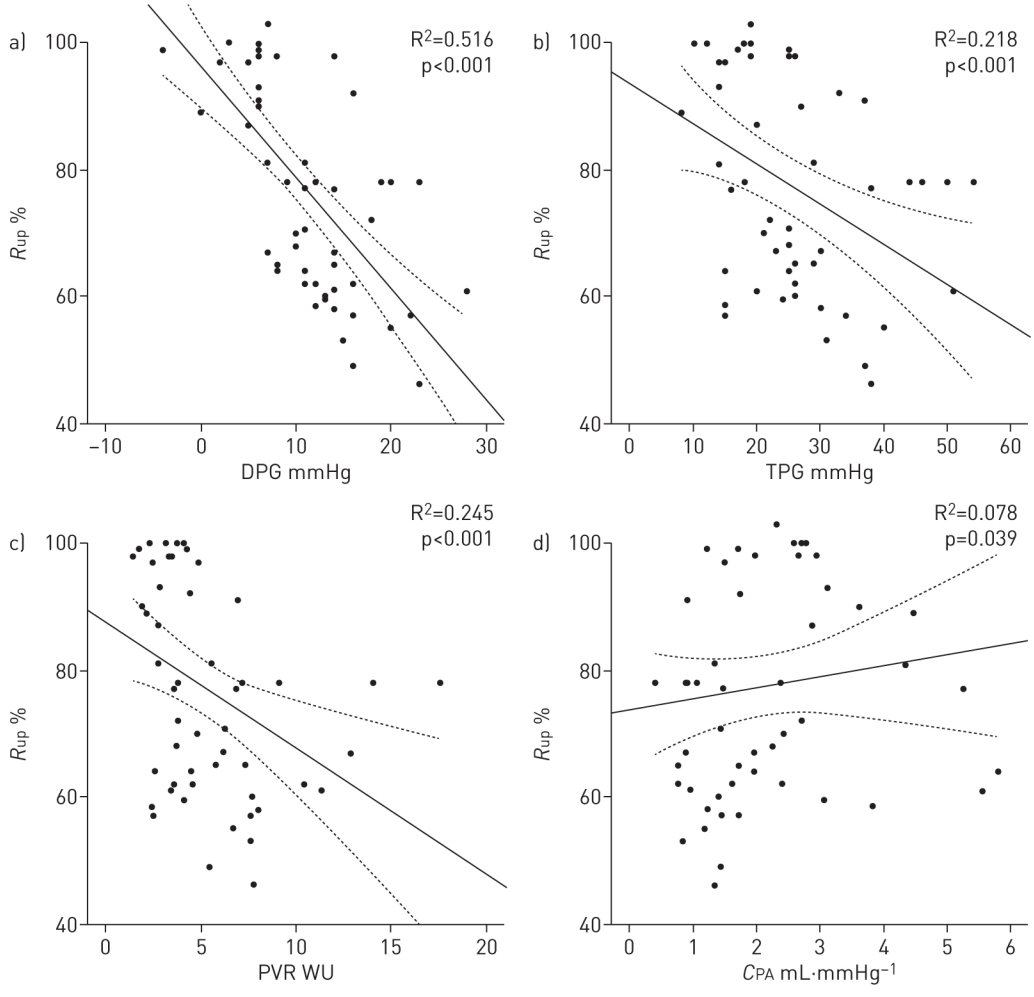

FIGURE 4 Relationship between upstream resistance (R_{up}) and parameters of right ventricular afterload in pulmonary hypertension due to left heart disease: a) diastolic pulmonary vascular pressure gradient (DPG), b) transpulmonary gradient (TPG), c) pulmonary vascular resistance (PVR) and d) pulmonary arterial compliance (C_{PA}). WU: Wood units. Data are presented as means and 95% confidence intervals of the linear regression functions.

evidence of small vessel disease in Cpc-PH resembling iPAH [2]. Ipc-PH showed very high R_{up} (figure 3c), indicating a passive increase in PVR and PAP driven by elevated left-sided filling pressures. To identify the best haemodynamic predictor of increased downstream stiffness and pulmonary vascular disease in PH-LHD, we performed regression analyses including PVR, C_{PA}, TPG, DPG and R_{up}. We found a strong negative correlation between DPG and R_{up}, while TPG, PVR and C_{PA} correlated only weakly with R_{up} (figure 4). Interestingly, R_{up} was not different between Ipc-PH patients with DPG <7 mmHg and PVR ⩽3 WU (n=6; R_{up} 96.9±4.2%; p=0.479; supplementary figure SA) and those with DPG <7 mmHg and PVR >3 WU (n=14; R_{up} 95.3±5.3%). These results suggest that DPG appears to be more sensitive than PVR and C_{PA} for the detection of changes in the downstream compartment, and might therefore be more meaningful for the definition of pulmonary vascular disease in PH-LHD.

Vasoreactivity in heart failure has been studied in the past using systemic infusions of nitrates and prostaglandin E_1 [11, 34–37]. In a more recent study in patients with heart failure with reduced ejection fraction, greater improvements in PVR, DPG and TPG could be observed in Cpc-PH compared with Ipc-PH [11]. However, prostaglandin E_1 and nitrates lower systemic blood pressure and increase CO. We performed selective pulmonary vasoreactivity testing using iNO. Patients with Cpc-PH showed significant improvements in right ventricular afterload during NO inhalation (table 2 and figure 5), but this was not the case in patients with Ipc-PH. The proportion of patients fulfilling classic haemodynamic responder criteria was similar in Cpc-PH (8.6%) and iPAH (9.7%). Interestingly, iNO led to significant improvements in right ventricular afterload in Cpc-PH irrespective of haemodynamic responder status (supplementary table SA). These findings may explain the significant haemodynamic response of Cpc-PH

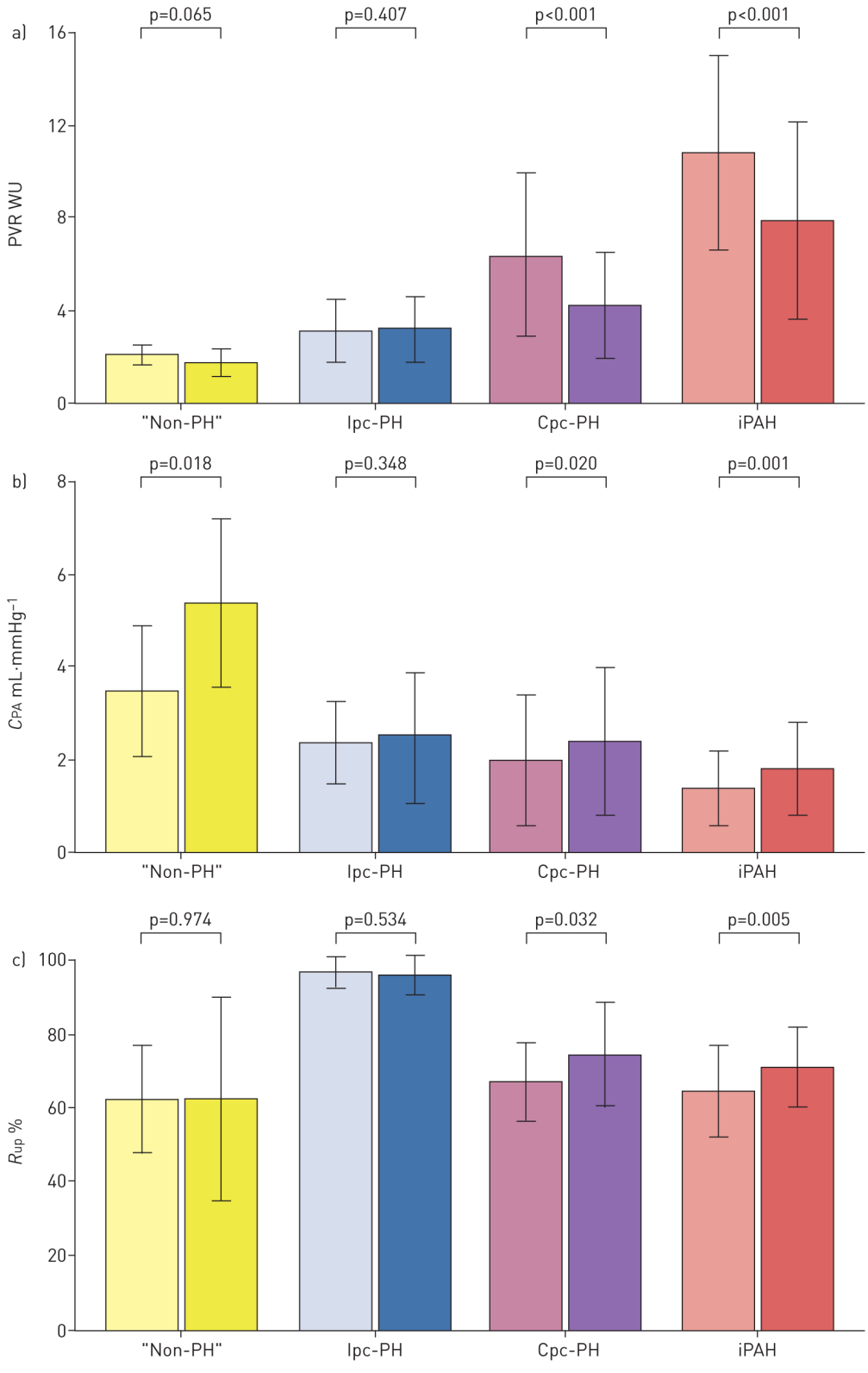

FIGURE 5 Effect of inhaled nitric oxide (iNO) on right ventricular afterload: a) pulmonary vascular resistance (PVR), b) pulmonary arterial compliance (C_{PA}) and c) upstream resistance (R_{up}) at baseline (lighter bar in each column) and after iNO (darker bar in each column) in patients with normal pulmonary haemodynamics (without pulmonary hypertension ("Non-PH")), isolated post-capillary PH (Ipc-PH), combined post- and pre-capillary PH (Cpc-PH), and idiopathic pulmonary arterial hypertension (iPAH). WU: Wood units. All p-values are results from paired samples t-tests.

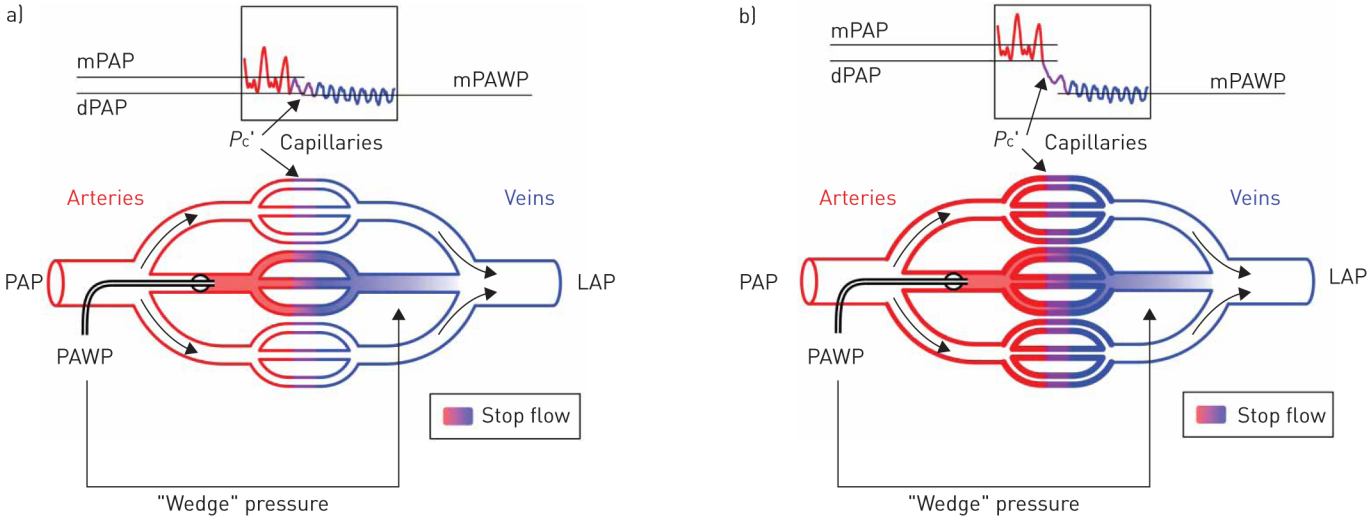

FIGURE 6 Models of the pulmonary circulation with corresponding phenotypes of pressure decay curves in a) isolated post-capillary pulmonary hypertension (Ipc-PH) and b) combined post- and pre-capillary PH (Cpc-PH). In Ipc-PH, there is a rapid decay from pulmonary arterial pressure (PAP) to pulmonary arterial wedge pressure (PAWP). The pressure in pre-capillary small pulmonary arteries and pulmonary capillaries ($P_{c'}$) is determined by left atrial pressure (LAP), and is at the same level as mean PAWP (mPAWP). In contrast, the pressure decay from PAP to PAWP is slow in Cpc-PH. $P_{c'}$ is markedly elevated in comparison to mPAWP due to an additional component of pulmonary vascular disease at the level of small pulmonary arteries and capillaries. mPAP: mean PAP; dPAP: diastolic PAP. Upstream resistance R_{up}=(mPAP–$P_{c'}$)/(mPAP–mPAWP)×100.

patients in the single positive randomised trial of sildenafil in PH-heart failure [38]. However, the study by GUAZZI *et al.* [38] was an exploratory trial with haemodynamic and echocardiographic end-points, and to date no positive randomised controlled trial with outcome data has been reported in PH-LHD [39–41]. Furthermore, in the recent randomised controlled MELODY-1 study, macitentan was associated with an increased incidence of significant fluid retention *versus* placebo in patients with Cpc-PH [42]. In addition, macitentan resulted in no significant changes in N-terminal pro-brain natriuretic peptide and PVR.

Limitations

The number of patients with iPAH and Cpc-PH in relation to Ipc-PH is overrepresented in this study, because the inclusion of patients with Ipc-PH was halted at a sample size of 20 patients, while inclusion of iPAH and Cpc-PH patients was continued. Data from vasoreactivity testing of classic responders should be interpreted with caution because only three Cpc-PH and three iPAH patients fulfilled the traditional haemodynamic responder criteria. Biexponential fitting of the decay curve may be affected by the presence of high "v" waves in PAWP tracings in case of atrial fibrillation and mitral regurgitation. In addition, arrhythmia in atrial fibrillation may alter the time-dependent algorithm for the derivation of $P_{c'}$. Therefore, patients with atrial fibrillation and other forms of arrhythmia at the time of haemodynamic assessment were excluded from our analyses, and only one Cpc-PH patient and three Ipc-PH patients had significant mitral regurgitation.

Another problem is that many haemodynamic parameters, such as TPG, pulmonary pulse pressure, ejection fraction, dP/dt_{max}, *etc.*, are load dependent. For PVR it has been shown that the relationship between pressure gradient and flow is linear. Furthermore, modulation of flow and pressure using dobutamine infusion in dogs had no effect on the partitioning of PVR [43]. Hence, a change in loading conditions of the pulmonary vascular system does not seem to influence the evaluation of the upstream component of PVR. For TPG, a flow- and LAP-dependent increase has been described, while DPG has been shown to be rather insensitive to these haemodynamic variables [29].

Conclusions

Our data show that increased right ventricular afterload is driven by elevated LAP in Ipc-PH and aggravated by pulmonary small vessel disease in Cpc-PH. Cpc-PH is responsive to iNO. The easiest haemodynamic parameter to assess the presence of pulmonary vascular disease in PH-LHD is DPG, which may serve as a surrogate for R_{up}, while PVR should be used with caution. Taken together, our in-depth analysis provides physiological support for current definitions of PH-LHD subtypes.

Conflict of interest: C. Gerges reports grants from United Therapeutics Corporation, Bayer HealthCare and Actelion Pharmaceuticals, during the conduct of the study. He has also received personal fees (for scientific symposia) from

GlaxoSmithKline, AOP Orphan and Actelion, outside the submitted work. M. Gerges reports grants from United Therapeutics Corporation, Bayer HealthCare and Actelion Pharmaceuticals, during the conduct of the study. He has also received personal fees (for scientific symposia) from GlaxoSmithKline, AOP Orphan and Actelion, outside the submitted work. P. Fesler reports personal fees (travel and accommodation support) from Actelion, outside the submitted work. I.M. Lang reports grants from United Therapeutics Corporation, Bayer AG and Actelion Pharmaceuticals, during the conduct of the study. She also received grants, personal fees and nonfinancial support from Actelion, AOP Orphan Pharmaceuticals, Bayer AG, GlaxoSmithKline, Pfizer and United Therapeutics Corporation, as well as honoraria from AstraZeneca, Servier, Cordis, Medtronic and Novartis, outside the submitted work.

Support statement: This research was funded by educational grants from Actelion Pharmaceuticals Ltd (00283GMS&C), Bayer HealthCare Pharmaceuticals (15662) and United Therapeutics Corporation (REG-NC-002). Funding information for this article has been deposited with the Crossref Funder Registry.

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